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Neurobiological basis of relapse prediction in stimulant-induced psychosis and schizophrenia: the role of sensitization

K Yui[1], K Goto[2], S Ikemoto[3], T Ishiguro[1], B Angrist[4], GE Duncan[5], BB Sheitman[5], JA Lieberman[5], SH Bracha[6] and SF Ali[7]

[1]*Department of Psychiatry, Jichi Medical School, Tochigi 329–0498, Japan;* [2]*Nippon Veterinary and Animal Science University;* [3]*Department of Legal Medicine and Human Genetics, Jichi Medical School, Tochigi 329-0498, Japan;* [4]*Psychiatry Service, New York VA Medical Center/NYU School of Medicine, New York, NY 10010, USA;* [5]*Department of Psychiatry, University of North Carolina School of Medicine, Chapel Hill, NC 27599-7166, USA;* [6]*VA Pacific Center for PTSD, Honolulu, HI, USA;* [7]*Neurochemistry Laboratory, Division of Neurotoxicology, National Center for Toxicological Research/FDA, Jefferson, AR 72079–9502, USA*

A number of consistent clinical observations provide direction for the hypothesis that pathological sensitization of neuronal systems may be an important factor for relapse or the onset of stimulant-induced psychosis (eg, methamphetamine or amphetamine psychosis, cocaine psychosis and phencyclidine psychosis) and schizophrenia. First, psychotic symptoms can be produced in normal subjects by stimulants. Secondly, a large portion of schizophrenic patients exhibit exacerbation of psychotic symptoms in response to stimulants at doses which would not be psychotogenic in normal subjects. Lastly, the ability of stress to precipitate the onset and relapse of schizophrenia is well documented. In this regard, acute responses to stimulants provide useful information for relapse prediction of schizophrenia and substance abuse. This paper addresses the nature and role of pathological sensitization in relapse of stimulant- and phencyclidine-induced psychosis and schizophrenia, and its relation to pathophysiology of schizophrenia.

Keywords: sensitization; stimulant; methamphetamine psychosis; spontaneous recurrence; stress; cocaine psychosis; noradrenaline; dopamine; schizophrenia; phencyclidine; rotational behavior

Spontaneous recurrence of methamphetamine psychosis

Drs Yui K, Goto K, Ikemoto S, Ishiguro T (Department of Psychiatry, Jichi Medical School, Tochigi, Japan): Amphetamine (AMP), methamphetamine (MAP) or cocaine can not only exacerbate schizophrenia[1,2] but induce paranoid-hallucinatory psychosis[3–5] during the acute or chronic intoxication phase in nonschizophrenic subjects.[1–5] The short-lived paranoid-hallucinatory states characterized by vivid visual hallucinations and the absence of thought disorder without marked reduction in levels of functioning in AMP or MAP psychosis appear to be distinct from the activation of schizophrenia.[6] Spontaneous recurrences of AMP- or MAP-induced paranoid-hallucinatory psychosis occasionally occur in subjects with a previous history of MAP psychosis in response to stress.[7,8]

AMP induces enduring sensitization to stress via changes in dopaminergic systems. This stress sensitization may help explain why psychosis only recurs in subjects with a history of AMP psychosis following exposure to stress.[9] Previous exposure to stressful stimuli induces noradrenergic hyperreactivity to subsequent mild stress.[10] Stress-induced noradrenergic hyperactivity may be a precipitating factor in stress-related psychiatric disorders.[11] It is therefore possible that sensitization to stress associated with noradrenergic hyperactivity and dopaminergic changes may be central to the development of spontaneous recurrences of MAP psychosis (flashbacks). To elucidate this possibility, we examined predictors and plasma monoamine metabolite levels in subjects with flashbacks due to previous MAP psychosis.

The subjects were 79 physically healthy females recruited from the inmates at a women's prison, including 45 with a history of MAP psychosis, eight subjects with persistent MAP psychosis which persisted for at least 6 months prior to blood collection, and 26 controls (19 MAP users and seven non-users,

Correspondence: SF Ali, PhD, Head, Neurochemistry Laboratory, Division of Neurotoxicology, National Center for Toxicological Research/FDA, Jefferson, AR 72079-9502, USA. E-mail: sali@nctr.fda.gov

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none of whom became psychotic). All subjects, except for the seven non-user controls who had been incarcerated for theft ($n = 4$), involuntary manslaughter ($n = 2$) and arson ($n = 1$), had been imprisoned for violation of the Stimulant Drug Control Law. They had not abused other substances, nor had they experienced any psychiatric disorder in the absence of MAP or other substances. All freely gave informed consent. MAP psychosis was diagnosed according to the DSM-IV (1994) criteria for AMP-induced psychotic disorder, based on a structured interview and inmate record review. Flashbacks due to previous MAP psychosis were defined according to the DSM-IV criteria[12] for hallucinogen persisting perception disorder (flashbacks) and a general definition of psychedelic drug flashbacks,[13] as a spontaneous recurrence of MAP-induced paranoid-hallucinatory states after a period of normalcy during which the pharmacological effects of MAP had worn off. Of the 45 subjects with a history of MAP psychosis, 29 experienced flashbacks during their incarceration in the prison (flashbackers) and the other 16 did not (non-flashbackers). The subject subgroups were age-matched ($P = 0.20$–1.00).

Thirteen of the 29 flashbackers were maintained on haloperidol (1–6 mg day^{-1}), chlorpromazine (50–75 mg day^{-1}) or thioridazine (30–75 mg day^{-1}) for 4 weeks before and during the study (medicated flashbackers). The other 16 flashbackers received the above neuroleptic treatment after blood collection during flashbacks, because of flashback aggravation (later-medicated flashbackers). Subjects were free of any other neuroleptic treatment or medication.

All subjects were strictly prevented from taking MAP and other substances for 3 months before and during the study. This was verifiable because of their confinement, which entailed repeated searches for contraband. Venous plasma was examined for the presence of MAP in eight randomly selected flashbackers at the time the flashbacks occurred using gas chromatography/mass spectrometry, as described previously;[7] all analyses were negative.

Data on stressful experiences during previous MAP use and factors triggering flashbacks were obtained from structured interviews. The criteria for stressful events were based on whether the events met the DSM-III-R criteria[14] for a severe to catastrophic type of psychosocial stressor. The criteria for frightening psychotic symptoms (perception of threat) were based on whether the subjects had been overwhelmingly threatened and whether they had taken refuge nearby.

The subjects received a low-monoamine, alcohol-free, and caffeine-restricted diet. Blood was obtained twice from the 29 flashbackers: once during the most prominent flashback states (within 14 days of the occurrence of flashbacks), and again within 30 days after the flashbacks resolved, and once from the other subjects upon admission to the prison by venipuncture after a 20-min rest. Plasma was assayed for: norepinephrine (NE) and its metabolite normetanephrine (NM), epinephrine (E), dopamine (DA) and its metabolites 3-methoxytyramine (3-MT), homovanillic acid (HVA) and dihydroxyphenylacetic acid (DOPAC) using HPLC-ECD, as previously described:[7] with a sensitivity of 0.01 pmol ml^{-1}, except for NM at 0.05 pmol ml^{-1}. The intra-assay and interassay coefficients of variation averaged 10.4% and 19.3%, respectively.

All monoaminergic values were subjected to the square-root transformation, rendering the distribution normal. The transformed values were analyzed using one-way analysis of variance (ANOVA) followed by post hoc tests. Moreover, the transformed values from the 29 flashbackers were analyzed using a repeated measures ANOVA with the presence or absence of neuroleptics as between subjects factor and flashbacks and no flashbacks as the within subjects repeated factor. Comparisons between subjects subgroups were performed using the Mann–Whitney U tests and the χ^2 tests.

Clinical characteristics of flashbacks

All subjects, except for the seven non-user controls, had abused MAP by means of one to 10 intravenous injections of MAP (30–50 mg per injection) per day during their previous periods of abuse. The flashbackers exhibited a reactivated MAP psychosis, without reexperiencing the stressful events, or the symptoms of PTSD or acute stress disorder. During flashbacks, all flashbackers continued to experience paranoid delusions, in which they developed transient auditory and visual hallucinations. Paranoid delusions abated after 3–282 days. Thus, the total duration of flashbacks was 3–282 days (mean ± s.d. = 65.8 ± 65.1 days). Considering that psychedelic drug flashbacks persisted for 1–2 years[13] or 5 years or longer,[12] the total duration may not be very long for flashbacks.

Increased sensitivity to stress associated with a predominance of noradrenergic over dopaminergic hyperactivity

Stressful experiences and reactivity to stressors The 29 flashbackers had been exposed to significantly greater numbers of threatening events (20 of the 29 flashbackers *vs* one of the 16 non-flashbackers, $\chi^2 = 7.10$, 1 d.f., $P<0.01$) and frightening psychotic symptoms (21 flashbackers *vs* one non-flashbacker, $\chi^2 = 7.50$, 1 d.f., $P<0.01$) than the non-flashbackers. The threatening events corresponded to severe or extreme types of psychosocial stressor: severe type ($n = 5$) included divorce ($n = 2$), rejecting parents ($n = 2$) or unwanted pregnancy ($n = 1$); extreme type ($n = 15$) included physical ($n = 14$) or sexual abuse ($n = 1$) by a companion in drug use. Frightening psychotic symptoms included auditory hallucinations threatening the subject with death ($n = 14$), frightening visual hallucinations ($n = 7$), delusions of being killed by persons concerned ($n = 5$), or delusions of being pursued by a gangster or the police ($n = 11$). The nine flashbackers who had not been exposed to threatening events had experienced such frightening psychotic symptoms. The dominant factors that triggered a total of 62 flashbacks were a mild fear of other people ($n = 55$, 88.7%): conflicts with inmates ($n = 24$), fear of other inmates

Table 1 Plasma levels of norepinephrine (NE), epinephrine (E), 3-methoxytyramine (3-MT) and dopamine (DA)

Subject subgroups	*Age*	*NE*	*E*	*3-MT*	*DA*
Flashbackers during flashbacks	28.2 ± 5.6	0.63 ± 0.61[a,b,c,e,f]	0.37 ± 0.51	1.38 ± 2.06[d]	0.08 ± 0.15
Medicated flashbackers	27.6 ± 4.5	0.71 ± 0.68[e,g]	0.29 ± 0.44	0.94 ± 1.52	0.15 ± 0.19
Later-medicated flashbackers	28.7 ± 6.4	0.56 ± 0.55[d,f]	0.44 ± 0.58	1.71 ± 2.38[d,h]	0.03 ± 0.08
Flashbackers during remission	28.3 ± 5.8	0.34 ± 0.35	0.38 ± 0.52	0.73 ± 1.44	0.17 ± 0.28
Medicated flashbackers	27.6 ± 4.4	0.41 ± 0.38	0.45 ± 0.48	1.05 ± 1.90	0.12 ± 0.18
Later-medicated flashbackers	28.9 ± 6.9	0.29 ± 0.33	0.33 ± 0.55	0.46 ± 0.90	0.21 ± 0.34
Non-flashbackers	28.9 ± 8.9	0.34 ± 0.34	0.57 ± 1.06	1.16 ± 2.25	0.11 ± 0.17
Subjects with persistent MAP psychosis	25.5 ± 2.5	0.60 ± 0.45[d]	0.49 ± 0.86	0.45 ± 0.93	0.15 ± 0.23
User controls	28.1 ± 4.3	0.22 ± 0.34	0.48 ± 1.28	0.13 ± 0.55	0.09 ± 0.14
Non-user controls	30.6 ± 7.3	0.16 ± 0.13	0.28 ± 0.36	0.70 ± 1.13	0.21 ± 0.28

Mean values ± s.d. pmol ml^{-1}. [a]$P<0.05$ *vs* remission (repeated measures ANOVA); [b]$P<0.05$ *vs* remission; [c]$P<0.05$ *vs* the non-flashbackers; [d]$P<0.05$; [e]$P<0.01$ *vs* the user controls; [f]$P<0.05$; [g]$P<0.01$ *vs* the non-user controls; [h]$P<0.05$ *vs* the medicated flashbackers.

($n = 7$), fear of disciplinary punishment ($n = 3$), fear of emitting body odor ($n = 4$), fear of the prison staff ($n = 14$), fear of husband ($n = 4$). These factors represent the level of ordinary stressors in the prison, meeting the DSM-III-R criteria for a mild type of psychosocial stressor.

Plasma monoamine metabolite levels Repeated measures ANOVA of the square-root transformed data in the 29 flashbackers revealed a significant difference between flashbacks and remission in only plasma NE levels (F [1, 27] = 8.27). There was no significant effect of neuroleptic treatment on plasma levels of NE and other monoamine metabolites. No significant interaction (flashbacks × neuroleptic treatment) was recognized for plasma levels of NE and other monoamine metabolites. Plasma NE levels during flashbacks were significantly higher than during remission, and were significantly higher than in the non-flashbackers and the user and non-user controls. Plasma 3-MT levels during flashbacks were significantly higher than in the user controls. Plasma NE levels in the subjects with persistent MAP psychosis were significantly higher than in the user controls. During flashbacks, both the 13 medicated and 16 later-medicated flashbackers had significantly higher NE levels than the user and non-user controls even though plasma NE or other monoamine metabolite levels did not differ significantly between the two subgroups during flashbacks and remission. The later-medicated flashbackers had significantly higher 3-MT levels than the medicated flashbackers and the user controls (Table 1).

Increased sensitivity to stress and the occurrence of flashbacks The flashbackers had been exposed to threatening experiences during previous MAP use. The dominant factor triggering flashbacks was a mild fear of other people. The present findings on plasma monoamine metabolite levels suggest that increased noradrenergic activity be related to the occurrence of flashbacks. Considering that stressful stimuli induce noradrenergic hyperreactivity to subsequent stress,[10] and that AMP induced enduring sensitization to stress,[9,15] threatening experiences together with MAP use may have increased sensitivity to subsequent exposure to similar but less severe situations, so that heightened NE release may have been elicited in response to a mild fear of other people.

It has been documented that 3-MT levels in the rat brain serve as a sensitive index of dopamine release.[16] It is most probable that 3-MT is formed peripherally and transported into the brain, implying an important correlation between plasma and brain 3-MT levels.[17] Thus, the elevated 3-MT levels during flashbacks may in some way reflect increased dopaminergic activity. Stressful stimuli have been found to sensitize 3-MT release.[18] Taken together, stressful experiences together with MAP use may have further induced some degree of increased sensitivity to stress in dopaminergic systems. Stress sensitization, acting through noradrenergic systems, may lead to pathological retrieval of traumatic events.[19] Reproducing noradrenergic hyperactivity can elicit traumatic memories following exposure to residual traumatic memories.[20] AMP-induced sensitization to stress in dopaminergic systems may be related to the enduring hypersensitivity to the psychotogenic effects of stress in spontaneous recurrences of AMP psychosis.[9] Therefore, a mild fear of other people may have elicited memories of MAP psychosis related to threatening experiences through increased sensitivity to stress associated with a predominance of noradrenergic over dopaminergic hyperactivity. As a result the flashbacks may have been triggered.

Plasma monoamine metabolite levels do not accurately reflect brain monoamine neurotransmitter activity, however, plasma NE[21] and 3-MT[17] levels can reflect gross changes in whole brain noradrenergic and dopaminergic metabolism, respectively.

Clinical studies have shown that haloperidol[22] or chlorpromazine[23] decreased plasma NE levels, and that thioridazine[24] had no significant effect on peripheral noradrenergic activity. Preclinical studies have reported that haloperidol or chlorpromazine had no significant effects on brain 3-MT levels.[25] In this study,

there was no evidence of neuroleptic treatment for any monoamine metabolite level. Both medicated and later-medicated flashbackers had significantly higher NE levels during flashbacks than the user and non-user controls. The later-medicated flashbackers had significantly higher 3-MT levels during flashbacks, in which they did not yet receive neuroleptic treatment, than the medicated flashbackers and the user controls. Thus, our neuroleptic treatment might not be a significant factor in raising the NE and 3-MT levels.

Acute CNS stimulant response as a predictor of relapse in schizophrenia and cocaine addiction

Dr Angrist B (New York VA Medical Center and NYU School of Medicine, New York): The CNS stimulant drugs are indirect catecholaminergic agonists that exert their effect by acutely increasing synaptic neurotransmitter concentrations. Since catecholamines are known to play important roles in 'positive' psychotic symptoms and the reinforcing effects of drugs of abuse, a number of investigators have hypothesized that acute responses to CNS stimulants might provide useful predictive information for future clinical events in schizophrenia and substance abuse.

CNS stimulant response as a predictor of relapse vulnerability in schizophrenic patients not taking neuroleptics

CNS stimulant drugs were administered to schizophrenic patients as long ago as the late 1930s.[26,27] Some patients showed increased psychotic symptoms. In the studies done since that time, the frequency of this response has been quite variable. These studies have been reviewed in detail,[28] and it has been calculated that, overall, approximately 40% of schizophrenic patients show increased psychotic symptoms after administration of CNS stimulant agents.[28]

Simultaneously, during the 1960s and 1970s, consistent data emerged indicating that chronic neuroleptic treatment contributed to the development of tardive dyskinesia. These data gave a sense of urgency to identifying individual patients who could remain neuroleptic-free. Clinical predictors for individual patients would have been extraordinarily valuable.

In the late 1970s and early 1980s, several investigators recognized that the response of schizophrenic patients to CNS stimulant 'challenges' might prove to be such a predictor. Since both CNS stimulants and neuroleptic discontinuation had 'pro-dopaminergic' effects, there might be some neurobiological overlap between these two stressors. More importantly, the first modern studies of CNS stimulants in schizophrenia[29] had shown that the pro-psychotic response to methylphenidate was state-dependent. Patients whose symptoms worsened when they received methylphenidate in the acute phase of their illness no longer showed psychosis exacerbation when challenged after they had attained remission. It seemed possible that CNS stimulants might prove to be a probe that would reveal a stable state in which neuroleptics were not needed.

Four groups have completed such studies.[1,30–32] In addition, at least two preliminary reports were published by two of the groups based on data overlapping their final reports.[2,33] van Kammen *et al*[30] challenged 13 patients with d-amphetamine 20 mg i.v. while they were still receiving pimozide, which was then discontinued. Six showed increased psychotic symptoms and seven showed no change. All six of the responsive patients relapsed within 20 days. Only one of the seven non-responders relapsed. Angrist *et al*[1] studied 25 patients withdrawn from fluphenazine decanoate. Six weeks after the last injection, a challenge of D-amphetamine 0.5 mg kg^{-1}, p.o. was given. Five of the 25 were considered responders (increased positive symptoms). Of these, all five relapsed within a month. Of the remaining 20 patients, three relapsed within that time. Lieberman *et al*[31] administered methylphenidate 0.5 mg kg^{-1} i.v. and placebo infusions both while patients were receiving neuroleptics and after neuroleptic withdrawal. Thirty-four patients were studied. Eleven were classified as responders, 23 as non-responders. Overall, survival rates were significantly lower in the responders than the non-responders over the next year. However, in the first month, only two of the 11 responders relapsed *vs* two of 23 non-responders. Thus, in this study, response did not necessarily predict rapid relapse. Davidson *et al*[32] administered a challenge of L-DOPA/carbidopa (250/25) four times daily to 28 patients who had not received neuroleptics in the prior month. Six patients met criteria for psychosis increase while 22 did not. Five of the six responders relapsed within a month *vs* four of the 22 non-responders.

One hundred patients participated. Twenty-eight were responders to the stimulant challenge of whom 18 relapsed within a month. Seventy-two patients were considered non-responders. Of these, 10 relapsed within a month. Chi-square analysis showed a highly statistically significant association between 'response' (increase in psychotic symptoms after a CNS stimulant 'challenge') and relapse within a month of neuroleptic discontinuation.

Sensitization to cocaine psychosis as a possible predictor of vulnerability for relapse to addiction

Sensitization, particularly to the behavioral effects of CNS stimulants, is an extraordinarily robust finding in preclinical studies (see Post *et al*[34] for review of sensitization to cocaine effects specifically). In clinical studies, two prior groups noted sensitization to the psychosis-inducing effects of cocaine.[35,36] In one study,[35] 67% of patients with primary cocaine dependence had experienced cocaine psychosis; in the second study, just over half had such psychoses.[36] In both studies, three-fourths of those patients who became psychotic described responses suggestive of sensitization—worsening of paranoia at the same or lower doses over time or onset of paranoia earlier in a binge.

We attempted to replicate these findings at our center. Because we wanted to focus the study on the psychosis-inducing effects of cocaine *per se* (not the

interaction between cocaine and psychosis-vulnerability factors), we attempted to exclude patients with a potential for psychosis for reasons other than cocaine exposure. We thus excluded patients whoever had psychotic symptoms while 'straight', who had psychoses induced by drugs other than cocaine (ie, PCP or hallucinogens) who showed evidence of schizotypy[37,38] or indeed had ever required psychiatric treatment, even for non-psychotic conditions. Clinically significant use of drugs other than cocaine (including alcohol, more than four drinks per 'binge') was also cause for exclusion. We studied 40 patients. Psychoses occurred in 47.5%. Just over 60% of these patients reported worsening of psychotic symptoms over time or onset at lower cumulative doses.[5]

While this latter study was being done, a paper was published that specifically proposed a link between sensitization and addictive behavior. Robinson and Berredge[39] proposed that sensitization of dopaminergic systems mediating appetitiveness, incentive and salience to drug-related cues and thoughts could induce a disregulated craving.

Since dopaminergic mechanisms are known to be important substrates for the stimulant-psychoses,[40] we reasoned that patients who had developed sensitization to the psychosis-inducing effects of cocaine might also be likely to have sensitization of the appetite 'incentive salience' system proposed by Robinson and Berredge.[39] Accordingly, we hypothesized increased relapse to addiction on follow-up in those of our patients who showed sensitization to psychosis-inducing effects of cocaine. Thirty-seven of 40 patients had been discharged at least 6 months at the time the follow-up was undertaken. Of these 37, 32 charts were obtained. These included 18 patients who had not experienced psychosis, five patients who showed paranoia but no sensitization and nine patients with paranoia and sensitization. The mean number of rehospitalizations for treatment of cocaine addiction was: non-paranoid, 0.28 ± 0.46; paranoid without sensitization, 0.00 ± 0.00; paranoid with sensitization, 0.78 ± 1.09. Statistical analysis showed a trend toward a larger number of rehospitalizations per patient among the sensitized paranoid patients.[5] These findings suggest that psychosis-sensitization may be a marker for more severe addiction, but one that is not overwhelmingly discriminating. Moreover, they have yet to be replicated. If this does occur, sensitization to cocaine psychosis may help identify patients at somewhat increased risk for addiction relapse.

Sensitization and schizophrenia

Drs Duncan GE, Sheitman BB, Lieberman JA (Department of Psychiatry, University of North Carolina School of Medicine, Chapel Hill): Evidence from studies of the longitudinal course of schizophrenia support a potential role for neurobiologic sensitization in the pathophysiology of the illness. From 30–60% of patients experience some progression of their illness, with psychotic relapse(s) resulting in lower levels of recovery and higher levels of residual symptoms.[41] The deterioration occurs predominantly in the early stages of the illness mostly in the first 5 years.[42] Some investigators have even suggested that the prepsychotic phase is the initial phase of deterioration.[43] Kraepelin's initial descriptions of the deteriorating course of schizophrenia are particularly relevant since they are based on the observations prior to the discovery of antipsychotic drugs. Evidence for a progressive deterioration has also been found in studies of first episode schizophrenia patients who were then followed prospectively from 1 to 5 years.[44–46] Those studies found that the length of time a person experienced psychotic symptoms in their first episode of illness, prior to receiving pharmacologic treatment, was a significant predictor of the time to treatment response,[44] relapse,[46] and long term outcome.[45] Specifically, the longer the duration of psychosis the poorer the treatment response and outcome. In addition, studies that followed patients over successive psychotic episodes of illness found that some of the patients took longer to recover or, in some cases, fail to recover as they had in their previous episode.[41,47] It was thus postulated that psychosis may reflect a pathologic process which diminishes the ability of the patients to respond to antipsychotic medication. The pattern of results is consistent with a process of pathologic sensitization.

Clinical experience with stimulants: support for the dopamine hypothesis

Although the studies of D_2 receptor occupancy by atypical antipsychotic drugs indicate that dopamine antagonist properties of the drugs can not completely explain their therapeutic actions, compelling support for the DA hypothesis of schizophrenia is found in studies of psychostimulants that potentate DA-mediated neurotransmission. It has long been recognized that amphetamine abuse can produce symptoms that mimic positive symptoms of schizophrenia.[6] In addition, controlled human studies involving drug-naïve volunteers have demonstrated that a psychotic state can be elicited by administration of small frequent oral doses of amphetamine.[48] Further evidence for stimulant-induced psychosis could be found in the methamphetamine abuse epidemic in Japan shortly after World War II.[49,50] At that time, huge military stores of methamphetamine found their way to the open market in Japan, which led to wide-spread abuse. A significant number of methamphetamine abusers developed psychosis that did not resolve with discontinuation of drug use; many patients required years for recovery.[50] The chronic psychoses induced by methamphetamine were clinically indistinguishable from paranoid schizophrenia, being characterized by vulnerability to psychotic exacerbation, with negative symptoms interspersed between psychotic episodes.

The controlled clinical studies with stimulant administration and experience with stimulant abusers indicated that repeated administrations of the drugs are required to induce psychotic symptoms. Work in experimental animals and humans has demonstrated

that repeated administration of stimulants produces a behavioral sensitization to subsequent drug exposure that persists long after discontinuation of the chronic treatment.[51] This sensitization phenomenon may involve both presynaptic and postsynaptic mechanisms, since increased release of dopamine in response to methamphetamine and increased behavioral responses to direct acting dopamine agonists have been demonstrated.[52] The progressive worsening of schizophrenic symptoms over time suggests that a sensitization process may also occur in this mental illness.

Lieberman *et al*[53] have suggested the mechanisms by which stimulant abuse could produce a chronic schizophrenic syndrome. They suggested that the initial aggravating event is enhanced dopaminergic activity that manifests as positive schizophrenic symptoms. Continued prolonged excessive dopaminergic activation is posited to induce neuronal degeneration in dopamine systems, leading to a hypodopaminergic state and negative symptoms. Indeed, chronic amphetamine treatment in rats is well-documented to be toxic to dopamine nerve terminals.[54] A reduction in dopamine could result in postsynaptic receptor supersensitivity, which would explain the re-emergence of positive symptoms after transiently increased dopamine availability, as occurs during stress or exposure to dopaminergic drugs.

In support of dopamine supersensitivity in schizophrenia, studies in which dopaminergic stimulants were administered to schizophrenic patients have demonstrated enhanced behavioral and neurochemical responses in comparison to healthy subjects, suggesting a sensitization of dopamine systems. Low doses of methylphenidate induced positive symptoms in stabilized schizophrenic patients but not in controls.[2,28] The phenomenon appears to be state dependent in that stable, nonpsychotic schizophrenic patients are less susceptible to develop transient psychosis compared to patients with active psychotic symptoms.[28] DA agonist administration has also been examined as a test to predict relapse in schizophrenia.[2,55] Stable nonpsychotic patients underwent provocative testing with DA agonists and then were followed prospectively after withdrawal of neuroleptic medications. Patients who had a transient psychotic symptom activation had a significantly shorter time to relapse than did patients who did not have symptom exacerbation. This was interpreted as a possible sign of an increased reactivity of DA neural systems in the patients who became psychotic after DA agonist stimulation.[2]

Additional evidence for enhanced dopamine sensitivity of DA systems in schizophrenia comes from elegant SPECT and PET studies that have measured D_2 receptor occupancy after amphetamine challenge.[56–58] Those studies involved functional imaging scans (SPECT or PET) using a competitive D2 antagonist as a radioligand before and after acute psychostimulant administration (eg, amphetamine, methylphenidate). The baseline scan provides a measure of D2 receptor number in the presence of basal concentrations of synaptic DA, while the post stimulant scan provides a measure of extracellular DA that has been released in response to the stimulants. The decrement in D_2 binding between the baseline and post drug stimulation provides an index of DA release and the concentration of synaptic DA. This approach has been validated in studies of human and sub-human primates.[56] If sensitization occurs in schizophrenia, one possible consequence predicted is that patients would exhibit elevated levels of presynaptic and/or extracellular DA. Results of studies from separate groups are consistent with this hypothesis.[57,58] They indicate that, compared to control subjects, patients with schizophrenia have greater decrements in D2 binding by ^{123}1-1BZM[58] and ^{11}C-11 raclopride.[57] However, patients in these investigations had previously received antipsychotic drug treatment, but were drug free at the time of study. Consequently, the possibility that the results could be due to treatment effects cannot be entirely ruled out. Nevertheless, this paradigm offers an existing new strategy to examine a hypothesized pathophysiological mechanism in psychosis.

The clinical and preclinical data described above suggest that there may be heuristic value in exploring the effects of chronic antipsychotic drug action on functional responses to dopamine agonists in rats, following chronic stimulant-induced sensitization paradigms. Such work could provide insight into neurobiological mechanisms of typical and atypical antipsychotic drug action and offer an experimental model to identify novel therapeutic agents.

Stress vulnerability and schizophrenia

The onset of schizophrenia is frequently precipitated by a stressful event and psychological stress is well documented to precipitate or exacerbate psychotic symptoms.[59] Furthermore, stress reduction strategies have significant impact on reducing relapse rates in schizophrenic patients.[60] Such observations suggest that schizophrenia develops when a threshold of stress tolerance in a vulnerable individual is exceeded. Moreover, some schizophrenic patients are susceptible to relapse due to psychological stressors, even while maintained on antipsychotic medication.[61] Stimulant abusers, similarly, have a propensity to experience a psychotic relapse in the context of psychological stress, even during periods of abstinence.[50]

Preclinical studies have demonstrated that stress stimulates dopamine release preferentially in the mesolimbic projection system.[62] Stress also increases glutamate release preferentially in the medial prefrontal cortex.[63] In metabolic mapping work,[64] stress was shown to increase 2-DG uptake and Fos induction in the medial prefrontal cortex. Interestingly, rats sensitized by chronic amphetamine, showed increased behavioral response to stress and exhibit greater increases in dopamine release in the medial prefrontal cortex in comparison to control rats.[65] Thus, a confluence of clinical and preclinical data implicates disturbances in stress-sensitive systems in the etiology of schizophrenia.

An integrated pathophysiological model of schizophrenia

The human brain may be endowed with a finite capacity for plasticity and neuronal modulation that is inherent in normally functioning neural networks, and available to compensate for perturbations that disrupt neural homeostasis.[66] When this capacity is exceeded, untoward responses, including pathologic forms of behavior may be manifest. In this context, schizophrenia may be the result of a sequence of events (specific failure in neural development) that begins with a congenital or early developmental deficiency in regulatory systems that normally compensate for variations in the levels and form of neuronal activity. As a result of this deficiency, patients with schizophrenia are more susceptible to the neurophysiological perturbations of environmental experiences that occur in the context of daily life, as their compensatory capacity is compromised and more easily exceeded. If prolonged or recurrent, such perturbations can lead to a persistent state of dysregulation, and potentially enduring pathologic changes, which are at first functional and ultimately structural.

Neurochemical sensitization This deficiency in neuronal modulatory capacity leads to the second pathophysiological stage that occurs in adolescence and early adulthood. During this period, stressful, but normative human experiences, (eg, family strife, going to college, entering military service) stimulate perturbations in neuronal activity that would otherwise be compensated for and equilibrium reestablished. However, with diminished regulatory capacity, progressive neurochemical sensitization occurs. This process underlies the prodromal, onset and deteriorative phases of the illness. A possible reason that the modulatory deficiency does not produce sensitization earlier (in childhood and early adolescence, though in some patients this does occur) may be due to the redundancy in neural synaptic connections that exists through adolescence, which temporarily compensates for the deficiency in modulatory capacity. The deficiency only becomes apparent when, in late adolescence, redundant synaptic connections are eliminated through neural pruning and the circuits refined to the point that the threshold of modulatory capacity is more easily exceeded.[67]

Another factor that contributes to the delay in the onset of psychosis in schizophrenia is the need for repetition and intermittency of neurochemical stimulation in response to environmental events that accrue over time, leading to a pathological sensitization. Grace[68] has suggested that physic (as opposed to tonic) DA release may be a neurophysiological correlate in schizophrenia to the intermittency of pharmacologic stimulation critical for induction of behavioral sensitization by DA agonists. Phasic DA release is dependent on VTA DA neuronal depolarization and impulse activity, and can result in an irregular burst firing pattern of large amplitude and transient increases in DA release.[69] Moreover, DA agonists such as stimulants potentiate impulse-dependent DA release,[70] while antipsychotic medications, which appear to interrupt the sensitization process in schizophrenia.[41,44] may exert their therapeutic effects by depolarization induced inactivation of DA cell firing.[71]

The sensitization process could involve maladaptive responses to stress. Stressors of mild intensity or duration selectively activate VTA neurons and produce DA release by mesocortical neurons in the prefrontal cortex, while more intense stressors also increase dopamine metabolism and release in the nucleus accumbens.[72] Prefrontal cortical efferents can regulate DA release in subcortical structures.[73] This effect can be blocked by administering NMDA antagonists or by lesioning of the amygdala or hippocampus,[74] suggesting that corticostriatal glutamatergic afferents activate stress-induced DA release.[75]

Dysregulation of inhibitory feedback mechanisms involved in the regulation of VTA neuronal activity may result in a pathological potentiation of impulse-dependent phasic DA release.[75] This pathological state then constitutes a new equilibrium between phasic and tonic DA mechanisms and persists even in the absence of further repetitive stimulation. Thus, when VTA neurons are again stimulated (by normative, stressful or pharmacologic stimuli) the phasic DA release is enhanced and excessive in the absence of normal inhibitory effects. In a similar fashion, limbic input to these neurons in the absence of effective corticostriatal regulation produces a greater influence on their firing. This results in a condition of behavioral sensitization which is associated with an increase in DA activity in the nucleus accumbens, and interestingly, a decrease in extracellular DA in the prefrontal cortex. This emphasizes the reciprocal relationship between the regulation of DA release in these two regions.[73]

A preexisting compromise in corticostriatal and temporolimbic pathways (such as might occur in schizophrenia as a result of the pathology in cytoarchitecture or synaptic connectivity) could produce a deficiency of tonic DA release in the nucleus accumbens. Such a condition of deficient corticostriatal glutamatergic innervation has been postulated by several investigators as occurring in schizophrenia by various mechanisms including decreased glutamatergic efferent projections and NMDA receptor hypofunction receptor.[73,75] This would facilitate the potentiation of phasic mesolimbic DA neuron activity, as well as postsynaptic responsivity and the eventual development of sensitization.[75] In this way prefrontal and temporal cortical deficits could facilitate the development of behavioral sensitization as it would appear to augment the mesolimbic response to stress as well as possibly to stimulants. Evidence consistent with this has been reported by Weinberger and colleagues. Chemical deafferentation of the prefrontal cortex by excitotoxin injection produced no significant alteration in basal DA levels or turnover in the basal ganglia or DA-related behaviors. However, markedly elevated DA mesolimbic activity was observed when the lesioned animals were exposed to stressful stimuli.[76] Similar results

have been found after surgical ablation of the prefrontal cortex. Therefore, animals with a functionally compromised prefrontal cortex have been found to experience relatively trivial environmental stresses as if they were life-threatening.[77]

In summary, the mesiotemporal and prefrontal cortical neuropathology (gross morphologic, cytoarchitectural and synaptogenic) that occur in schizophrenia may result in a pathological decrease in prefrontal cortical activity that could result in a prolonged decrease in tonic extracellular DA levels within the nucleus accumbens. This would ultimately lead to schizophrenic patients experiencing abnormally large phasic DA responses to behaviorally relevant stimuli.[75] This process would have explained a number of clinical phenomena including the pathogenesis of the illness onset, the association between psychotic episode duration and number and treatment response and the enhanced sensitivity to stress and psychostimulants of patients with schizophrenia.

Schizophrenia and circling behavior: from animals to man

Drs Ali SF[1], and Bracha HS[2] ([1]Neurochemistry Laboratory, Division of Neurotoxicology, NCTR/FDA, Jefferson, Arkansas, and [2]VA National Center for PTSD, Honolulu, Hawaii). Phencyclidine (PCP; angel dust) is one of the drugs of abuse known to produce psychotic effects and several schizophrenia-like symptoms such as hallucination, paranoia and emotional withdrawal and motor retardation in humans.[78–80] PCP-induced schizophrenia was first proposed over 35 years ago.[80] One of the most interesting effects of PCP in humans is that PCP-intoxicated patients can not be distinguished from schizophrenic patients on the basis of presenting symptoms alone.[81–83] In normal volunteers subanesthetic doses of PCP can produce an acute psychotic state for several hours, and overall behavioral symptoms resemble acute schizophrenic decompensation.[79] In animals, PCP causes a variety of behavioral changes which include changes in locomotor activity, stereotypes, ataxia, lateral head weaving, back pedaling and turning.[84–92] It has been reported that PCP induces ipsilateral rotation in rats after unilateral lesion with 6-hydroxydopamine,[93] suggesting that ipsilateral rotation may be mediated via presynaptic effects on dopamine neurons. In addition to PCP, other drugs of abuse such as amphetamine and cocaine also produce circling behavior in rats.[94–96] Hiramatsu *et al*[97] reported comparable behavioral and neurochemical effects of [(+)–5-methyl-10-11-dihydro-5H-dibenzo[a,d]-cyclohepten–5, 10-imine maleate] (MK-801) and PCP. Like PCP, MK-801, a non-competitive NMDA receptor antagonist, also produced several complex behavioral effects in rats, eg, lateral head weaving, body rolling and falling hyperlocomotion and ataxia.[98–100] Olney *et al*[101] reported that acute administration of PCP and related agents like MK-801, teletamin and ketamine produce acute pathomorphological changes in a specific population of neurons in rat brain. This neuropathological alteration in posterior cingulate cortex increased in the first 12 h and then gradually diminished over the next 12 h suggesting that it might be involved in the psychotic effects caused by PCP in humans.[101]

Circling behavior has recently been described in patients with severe psychotic symptoms.[102,103] Circling behavior is one of the best-understood behaviours in rodents and is thought to be mediated via dopaminergic pathways.[79,94,96,103,104,105] In the present study we evaluated circling pattern in schizophrenic patients and used that to develop an animal model where we examine the effect of acute injections of PCP or (+) MK-801 on circling preference in rats and on lateralization of activity in the dopamine system of the forebrain.

The subjects were 10 schizophrenic patients and 85 healthy adults who included physicians, students, and hospital employees at the University of California, San Diego. The inclusion and exclusion criteria for the subjects, and the procedure to quantitate the circling pattern by rotometer and data analysis have been previously described.[102] Each patient and each control wore the rotometer for about 8 h, starting between 8:00 and 9:00 am. Subjects were not given any specific instructions and were unaware of the type of counts obtained by the device. All 10 schizophrenic patients turned more to the left than to the right as compared with controls. The percent right preference was 49.9% + 11.3%, the patient's mean percent right preference was 30.7% + 14% (Figure 1a).

Animal study subjects were adult naive Sprague–Dawley female rats, approximately 10–12 weeks old, weighing 300 ± 10 g. The rats were randomly divided into groups for different experiments. Testing was conducted in a cylindrical glass enclosure with a 16″ diameter and a 10″ height. Each animal was placed in this cylinder and an observer who was unaware of the experimental conditions recorded circling behavior. Complete (360°) left or right rotations were counted before and after the drug (PCP or (+)-MK-801) administration. Two to three weeks later, the animals were injected again with the same dose of PCP or (+) MK-801, placed in the circling apparatus to observe the circling, and killed by decapitation 1 h after administration. Brains were rapidly removed, and each side of the striatum was dissected separately. In a follow-up experiment, two groups of animals were dosed with PCP or (+) MK-801, and killed 1 h after the dose administration. Brains were quickly removed, and each striatum was further dissected into medioventral, dorsolateral and globus pallidus, placed on dry ice and stored at −70°C for monoamine assays. Concentrations of dopamine and its metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), were quantified by a modified method of high performance liquid chromatography combined with electrochemical detection (HPLC/EC) as described by Ali *et al*.[106]

A single injection of (+) MK-801 in rats produced a dose-dependent increase of rotation, and the highest number of rotations was found at 0.1 mg kg^{-1} dose level. Injection of PCP or (+) MK-801 at different sites in the rat did not produce any difference in rotational

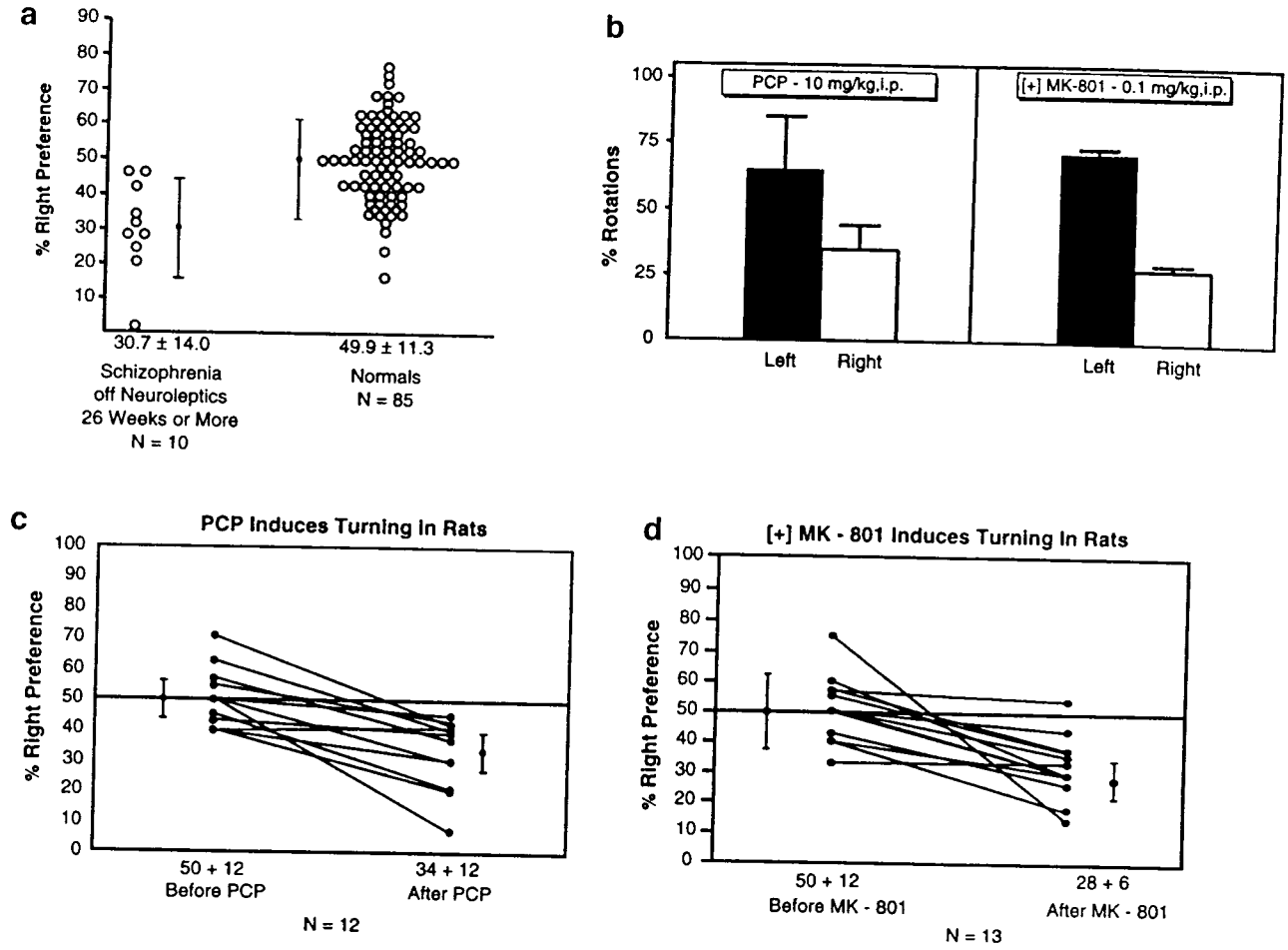

Figure 1 (a) Percent of spontaneous full (360°) turns to right (% right preference) during 8 h of automated monitoring. Male subjects, $P<0.0004$, Wilcoxon two-sample test. (b) Effects of a single injection of PCP or (+)-MK-801 on the circling preference presented as percent rotation in rats. $^*P<0.001$ significantly different between left and right rotation in both drugs. Percent of spontaneous full (360°) turns to right (% right preference) over a 2-h period after PCP (c) or (+)-MK-801 (d) administration in rats. Turning preferences were counted in each animal before and after the drug administration in (c) and (d). (Parts of the data were adopted and modified from Bracha[102] and Ali *et al*[106]).

behavior. At doses of 0.5 and 1.0 mg kg^{-1} (+) MK-801 the animals became less active and did not show any motor activity or rotational behavior. Similar effects were found with different doses of PCP. When rotational behavior was analyzed as a percent of turning preference, we found that following single injections of PCP (10 mg kg^{-1}) or (+) MK-801 (0.1 mg kg^{-1}), rats showed a preference to turn to the left (65% and 72%, respectively) (Figure 1b, c, d). Injection of (+) MK-801 produced an increase of dopamine metabolites (DOPAC and HVA) whereas PCP produced an increase of HVA concentration in whole striatum on both sides of the brain. However, these increases tend to be higher in the left than in the right side of the brain. In a follow-up experiment, the striatum was further dissected into medioventral, dorsolateral and globus pallidus from each side of the brain. The neurochemical analysis revealed that the concentration of HVA was increased bilaterally in the medioventral and dorsolateral region of the striatum. In contrast, in globus pallidus a significant increase in DA, DOPAC and HVA concentration was found only on the left side after PCP or (+) MK-801 administration.[106]

There have been consistent reports of PCP-induced psychotic behavior in humans[79,107] and circling behavior in rats,[88,94,108] however, in this study we found that not only PCP, but a noncompetitive NMDA receptor antagonist (+) MK-801, produces left-turning preference in rats, a finding similar to that found in human schizophrenics. There are reports in the literature that other drugs of abuse such as amphetamine and cocaine along with PCP produce circling behavior.[88,94,96,109] However, in this study we report that schizophrenic patients and administration of PCP and (+) MK-801 to rats produced predominately left circling. Javitt and Zukin[79] clearly summarized that the proportion of nonschizophrenic subjects who develop a psychotic state after acute administration of PCP is at least 25%, which is more than the rate of psychosis after acute exposure to amphetamine or methylphenidate. As opposed to amphetamine-induced psychosis, PCP-induced psychosis incorporated both positive (eg

hallucinations, paranoia) and negative (eg, emotional withdrawal, flat affect) schizophrenic symptoms. PCP-induced psychosis also uniquely incorporated the formal thought disorder and neuropsychological deficit associated with schizophrenia.[79] Bracha *et al*[103] also demonstrated a correlation between the severity of unmedicated schizophrenic patient's delusions and the severity of their left-turning behavior bias. They attributed the 'spontaneous, subtle preference for turning towards the left hemispace while moving around' which they monitored with a device worn by the patients during waking hours for several days, to 'inattention to the right hemispace'.

Our neurochemical data also demonstrate that single injections of PCP or (+) MK-801 increased the turnover of DA on both sides of striatum by increasing the concentrations of metabolites. Further dissection of striatum revealed that PCP and (+) MK-801 produced significant increases of dopamine and its metabolites, DOPAC and HVA, on the left side of the globus pallidus.[106] There are some reports suggesting left hemispheric dysfunction in patients with schizophrenia. These studies used evoked potentials, auditory threshold, electroencephalograph, performance on psychometric tests, signals from computerized tomography and hemispheric blood flow.[110–112] Early *et al*[111] used positron emission tomography (PET) to identify abnormalities in regional cerebral blood flow in newly-diagnosed, never medicated patients with schizophrenia. It is interesting to note that Early *et al*[111] found no other abnormalities except that patients had abnormally high blood flow in the left globus pallidus. This study correlated with our neurochemical finding of increased dopamine and metabolites on the left side of the globus pallidus.[106] In summary, our studies clearly demonstrate that schizophrenic patients turn preferentially to the left and animal study showed that PCP and a similar compound (+) MK-801, can produce a similar turning preference towards the left, and therefore, these behaviors in rats may be used as a model to further study the etiology of schizophrenia in humans. Furthermore, it is possible that this turning preference towards the left is due to an asymmetry in DA function found in the globus pallidus after administration of PCP and similar drugs.[106]

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